# mtDNA lineage analysis of mouse L-cell lines reveals the accumulation of multiple mtDNA mutants and intermolecular recombination.

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**Public Summary:**

**Scientific Abstract:**
The role of mitochondrial DNA (mtDNA) mutations and mtDNA recombination in cancer cell proliferation and developmental biology remains controversial. While analyzing the mtDNAs of several mouse L cell lines, we discovered that every cell line harbored multiple mtDNA mutants. These included four missense mutations, two frameshift mutations, and one tRNA homopolymer expansion. The LA9 cell lines lacked wild-type mtDNAs but harbored a heteroplasmic mixture of mtDNAs, each with a different combination of these variants. We isolated each of the mtDNAs in a separate cybrid cell line. This permitted determination of the linkage phase of each mtDNA and its physiological characteristics. All of the polypeptide mutations inhibited their oxidative phosphorylation (OXPHOS) complexes. However, they also increased mitochondrial reactive oxygen species (ROS) production, and the level of ROS production was proportional to the cellular proliferation rate. By comparing the mtDNA haplotypes of the different cell lines, we were able to reconstruct the mtDNA mutational history of the L-L929 cell line. This revealed that every heteroplasmic L-cell line harbored a mtDNA that had been generated by intracellular mtDNA homologous recombination. Therefore, deleterious mtDNA mutations that increase ROS production can provide a proliferative advantage to cancer or stem cells, and optimal combinations of mutant loci can be generated through recombination.

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